

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC25828A		FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/IB2004/004239		International filing date (day/month/year) 20.12.2004	Priority date (day/month/year) 31.12.2003	
International Patent Classification (IPC) or national classification and IPC C07D417/14, C07D413/14, C07D403/14, C07D409/14, A61P25/18, A61K31/404, A61K31/423, A61K31/428, A61K31/454, A61K31/4709, A61K31/55				
Applicant WARNER-LAMBERT COMPANY LLC et al.				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand 17.01.2005		Date of completion of this report 23.11.2005		
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Härtinger, S Telephone No. +49 89 2399-		



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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-133 as originally filed

Claims, Numbers

1-15 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application,
 - ☒ claims Nos. 11-15
- because:
- ☒ the said international application, or the said claims Nos. 11-15 with respect to IA relate to the following subject matter which does not require an international preliminary examination (specify):
see separate sheet
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☐ no international search report has been established for the said claims Nos.
 - ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
 - ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
 - ☐ See separate sheet for further details

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-15
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-15
Industrial applicability (IA)	Yes: Claims	1-10
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Section III

1. Claims 11-15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(I) PCT).

Section V

1. The application relates to D2/5-HT2 antagonists with antipsychotic activity. The relevant prior art has been indicated in the international search report together with the relevant passages.

D1: STRUPCZEWSKI J T ET AL: "3-(ARYLOXY)ALKYLPIPERIDINYL-1,2-BENZISOXA ZOLE S AS D2/5-HT2 ANTAGONISTS WITH POTENTIAL ATYPICAL ANTIPSYCHOTIC ACTIVITY: ANTIPSYCHOTIC PROFILE OF ILOPERIDONE (HP 873)" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 38, no. 7, 1995, pages 1119-1131, XP000941571 ISSN: 0022-2623

D2: HOWARD H R ET AL: "3-BENZISOTHIAZOLYLPIPERAZINE DERIVATIVES AS POTENTIAL ATYPICAL ANTIPSYCHOTIC AGENTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 39, no. 1, 5 January 1996 (1996-01-05), pages 143-148, XP000652318 ISSN: 0022-2623

D3: US-A-5 350 747 (HOWARD ET AL) 27 September 1994 (1994-09-27)

D4: EP-A-0 135 781 (HOECHST-ROUSSEL PHARMACEUTICALS INCORPORATED) 3 April 1985 (1985-04-03)

2. The novel structural feature of the present compounds resides from the present parameters X and W, which do comprise the carbonyl groups disclosed in D2 and D3. D1 and D4 do not disclose benzo fused nitrogen rings having acyl groups bonded to the ring nitrogen atom. In the light of this prior art, the claimed matter appears to have met the novelty requirements of Art. 33(2) PCT.

3. D1 teaches that the antipsychotic pharmacophore is represented by a structural fragment, which has all of the present formula 1 with the exception of the heterobi/tricycle on the right hand side of the formula. On page 1122 it is said, that the "tactic for further studying the structure-activity relationships within the series was to keep the 6-fluoro-3-(1-propyl-4-piperidiny)-1,2-benzisoxazole functionality constant while varying the aryloxy substituent bonded at the propyl terminus of the piperidine nitrogen". Heterobicyclic terminal groups have also been considered, such as the indolyl group, for which it was found, that the "receptor binding characteristics were similar to the lead compound". Based on this disclosure, the skilled person, who as looking for further anti-psychotic agents, was instructed to further modify the said terminal portion of the pharmacophore. He was confirmed in doing so through the activity tests disclosed in D2 (cf. page 145-146) and D4 (cf. Table 1), which proof that the qualitative ability to interact with the D2/5-HT2 receptors was not lost, even when a heterocycle is totally absent at the said terminal portion of the afore discussed pharmacophore. As such, the skilled person would have expected that a further structural modification at this molecular locus is without effect, at least when the qualitative properties of the compounds are considered. As such, starting from the indolyl derivatives disclosed in D1, and taking into consideration the overall teaching of D1-D4, the structural modifications done with respect to the benzo fused lactam compounds (i.e. the replacement of the lactam carbonyl group of, for instance, D2: compounds 5 to 8; D3: examples 38, 54, by a ring methylene group) is considered obvious. As the present application is silent about any further properties of the presently reduced nitrogen heterocycles, which have not already been disclosed in D1-D4, the claimed subject-matter does not appear to have met the inventive step requirements of Art. 33(3) PCT.

Section VI

1. The international patent applications D5 (= WO 2004/037819 A, PFIZER PRODUCTS INC; NORRIS, TIMOTHY; COLON-CRUZ, ROBERTO, 6 May 2004) and D6 (WO 2004/026864 A, WARNER LAMBERT CO [US]; ANDREANA TONJA LYNN [US]; CHO STEPHEN SUNG YON, 1 April 2004) have been published between the priority and filing date of the present application. By consequence, the N-acyl substituted derivatives disclosed therein do not form part of the state of the art as

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defined in the PCT. D5 and D6 have been disregarded from further consideration but may become relevant in the regional phase before the EPO.